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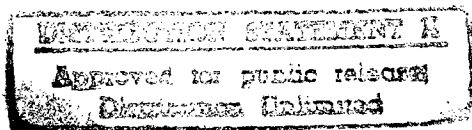
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CHARACTERISTICS OF THE REACTION OF THE GASTROINTESTINAL  
TRACT TO CHEMICAL STIMULATION UNDER CONDITIONS OF INJURY  
OF THE ORGANISM DUE TO RADIOACTIVE STRONTIUM

- USSR -

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CHARACTERISTICS OF THE REACTION OF THE GASTROINTESTINAL  
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Following is a translation of an article by  
G. A. Lebedeva in Arkhiv Patologii (Archives  
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21-28.

It is well known from the literature that the reactivity of the organism is changed when ionizing radiation acts on it. The majority of works which have been conducted in this direction have been devoted to the study of reactivity in the presence of X-ray irradiation. In the earlier investigations, where on the whole small dosages were used, a stimulating action of radiation was recorded (Freund, 1929; Fukase, 1930; Buhtz, 1932; B. N. Mogil'nitskiy and L. A. Gol'st, 1935); communications later appeared concerning a lowering of the reactivity of the organism in the presence of irradiation (V. V. Brunst, 1936, 1937; V. G. Garshin and co-workers, 1938; S. I. Matuskov, 1947; V. V. Shikhodyrov, 1957; A. Ye. Ivanov and V. F. Sosova, 1956).

There are only isolated communications in the literature pertaining to the question of the reactivity of the organism in the presence of injury due to radioactive substances. Thus, a lowering of the immunobiological properties of the organism in the presence of the administration of polonium is reported (B. B. Moroz and V. V. Vasil'yevskaya, 1957); a change in the reactivity of the intestine in the presence of injury due to this isotope is described (Z. I. Poluboyarinova, 1957). The present investigation was conducted with the purpose of studying the tissue reaction of the gastric and intestinal wall in animals, injured by strontium ( $\text{Sr}^{90}$ ).

The isotope in question (a B-radiator with a particle energy of 0.6 mev and a half-life period of 28 years) is one of the most widely distributed products of uranium fission and possesses considerable toxicity. When it gets into the organism, the strontium is deposited in the bony tissue. Its excretion proceeds chiefly via the gastrointestinal tract.

The experiments were conducted on 120 male white rats, which were administered  $\text{Sr}^{90}$  intraperitoneally in a quantity

of 0.4  $\mu\text{c/g}$  of weight. The activity utilized appears to be carcinogenic and evokes insignificant morphological changes in the gastrointestinal tracts. A 10 percent solution of acetic acid served as chemical stimulant and was administered to the rats on an empty stomach through a catheter into the stomach (1 ml), the small intestine (0.5 ml) and the preliminarily cleaned large intestine (0.5 ml) one month after the  $\text{Sr}^{90}$  lesion. The indicated concentration of the acid was selected experimentally in order not to cause the death of the animals. Rats not injured by  $\text{Sr}^{90}$ , in which a burn of the mucous membrane of the stomach and intestine was evoked by an analogous method, served as control. The control and the experimental animals were killed simultaneously at various periods (from the first to the 110th day) after the administration of the acid solution. The material was fixed in a 10 percent solution of neutral formalin and sealed in celloidin. The ordinary methods of staining histological sections were used.

In the stomach of the control rats, an inflammatory process developed in the mucous and submucous membranes when the solution was administered. It was accompanied by a change in the character of the secretion in the principal glands of the body of the stomach and by the appearance in them of granules of a mucoidal secretion. The acute inflammation subsided toward the seventh to tenth day. Residual phenomena in the form of infiltration with round cells and the appearance of groups of macrophages, containing hemosiderin, were observed up to 20-25 days. Restoration of the structure of the gastric wall was subsequently noted. In only one rat (on the fifth day) was erosion of the mucous membrane detected, and in two rats, "traces" of former erosions were detected in the form of sclerosis of the submucosa and accumulations of macrophages, containing hemosiderin.

In the animals injured by strontium, the inflammatory process was accompanied by the formation on the anterior and posterior walls of the body of the stomach of broad necroses and hemorrhages, embracing the entire mucous membrane. On the boundary with the zone of necrosis there appeared a leucocytic projection, in which on the third to fifth day a considerable breakdown of leucocytes and a further diminution of their number toward the 7-10th day was observed. Tearing off of the necrotic masses was retarded up to the 15-20th, and sometimes even the 90th day. At the site of tearing off there were left ulcers, the bottom of which was filled with granulation tissue. The latter was rich in cellular elements, the quantity of which, however, subsequently gradually diminished. On the 10th day collagenous

fibers appeared in the granulation tissue, and a considerable amount of sclerosis was noted later. Eosinophil and round cell infiltration was observed in the muscular and serous membranes for a long time (40-110 days). Epithelization of the ulcer ended in some animals toward the 25-30th day; in others it was not detected before the end of observations. Neoplastic glands, paved with mucoid cells, often had an unusual form and were located in the submucosa. In certain cases a considerable racemose proliferation of the glands was observed (Fig. 1). In the areas of the mucous membrane adjacent to the ulcers, dedifferentiation of the glandular cells and the appearance in them of granules of a mucoid secretion occurred. Goblet-shaped cells were encountered among the cells of the neoplastic epithelium (Fig. 2). Edema and cellular infiltration were observed in the submucosal layer (the latter was observed for the course of the entire period of epithelization).

Thus, the most pronounced changes in both groups of animals were observed in the region of the body of the stomach. However, this fact still fails to be a demonstration of the maximal sensitivity of the given section to the action of chemical factors. It is well known that when small quantities of cauterizing substances get into the stomach, the maximal changes arise in the region of the small curvature (Lewy, 1886; Haberda, 1895; Strohmeyer, 1912), since the liquid can not smooth out the creases of the mucous membrane and mechanically flows along the small curvature of the stomach (Ernst). When large quantities of chemical substances are taken, the maximal changes, as the investigations of N. A. Krayevskiy and V. S. Mayata (1938) show, are localized in the region of the pyloric section, and here it is not the increased sensitivity of the pyloric section which plays the basic role, but spasm of the musculature of the pylorus, holding back the gastric contents in its territory. The localization of the changes in the stomach of the animals which we investigated was determined, apparently, by the location of the catheter and by the direction of the stream of acid solution, being introduced under pressure and getting directly into the region of the body of the stomach.

After a burn of the mucous membrane granules of mucoid secretion appeared in the principal glands of the body of the stomach in rats of both groups. A similar reaction can arise in the presence of various pathological states (Yu. M. Lazovskiy with coworkers, 1948). Among the control animals the mucoid secretion was noted in the period from the third to the 15th day; in the experimental animals it was sometimes observed before the end of the investigation.



Fig. 1. Stomach of a rat, injured with  $\text{Sr}^{90}$ . Ninetieth day after the administration of the acid. Defect of the mucous membrane, filled with necrotic masses. Racemose proliferation of the glands. Sclerosis of the submucosal layer (hematoxylin-eosin stain. X 60).

Such a prolonged change of the character of the secretion is associated, probably, with suppression of the differentiation of the neoplastic mucoidal cells.

The racemose proliferation of the gastric glands, noted by us in the animals injured by  $\text{Sr}^{90}$ , is closely associated, apparently, with an inflammatory reaction. N. I. Churbanov (1940) considers that the nature of the heterotopic proliferations is always inflammatory. The growth of the epithelium deep down proceeds only when the underlying tissue is granulation tissue (V. G. Garshin, 1927). The changes noted attest concerning a certain defectiveness and distortion of the regeneration process.

By comparing the results obtained in the experimental and control groups, one can establish a raised vulnerability of the tissues in the animals injured by  $\text{Sr}^{90}$  and the appearance of broad foci of necrosis as a result of this.



Fig. 2. Stomach of rats, injured with  $Sr^{90}$ . Seventh day after the administration of acid. Goblet-like cells in the epithelium of the neoplastic mucous membrane (Stained with mucicarmine by the Meier method. X 60).

In the small intestine of the control rats, after the administration of the acid solution there arose an acute inflammation with the formation of superficial necroses and hemorrhages, destruction of the epithelium of the crypts, and leucocytic infiltration of the mucous membrane and the submucosal layer were observed. Tearing off of the necrotic masses began from the first day; epithelization of the erosions which had formed began from the second day, and ended on the fourth day. Residual phenomena in the form of round cell infiltration of the submucosa layer were noted on the fifth day. No changes in the intestine were observed subsequently.

Among the animals injured with  $Sr^{90}$ , as well as among the control animals, the development of an inflammatory process, the appearance of superficial necroses, hemorrhages, the destruction of the epithel-

ium of the crypts, was determined. The epithelization of the erosions, which had formed after tearing off the necrotic masses, began from the third and ended toward the seventh day. Irregularly located deformed villi were encountered in the neoplastic mucous membrane. Residual phenomena in the form of small accumulations of round cell elements in the submucosal layer were noted on the 10-15th day. No changes were subsequently determined.

It is evident from the data presented that changes in the small intestine are expressed consider-



Fig. 3. Large intestine of a control rat. The First day after the administration of acid. Acute inflammation. Necrosis and hemorrhages in the mucous membrane. Leucocytic infiltration of the submucosal layer (hematoxylin-eosin stain. X 100).

ably more weakly than in the stomach and the large intestine (see below). The epithelization of ulcers and the restoration of the structure of the mucous membrane set in here rather rapidly. The lesser susceptibility to injury, possibly, is explained by the fact that the acid administered is partially neutralized by the alkaline contents of this section. It is also well

known that the small intestine possessed a larger regenerative capacity in comparison with the other sections of the gastrointestinal tract (Friedman, Warren, 1942).

The comparison of the changes in the experimental and the control groups shows a later epithelization of the erosions in the experimental animals (those injured by strontium) and the appearance among them of atypically located villi in the neoplastic mucous membrane.

In the large intestine of the control rats after the administration of acid there developed an acute inflammation with the formation of superficial necroses and hemorrhages, and destruction of the epithelium of the crypts was observed (Fig. 3). On the third day necrotic masses were torn off into the lumen, on the fifth day -- epithelization of the erosions which had formed began. The destruction of the epithelium of the crypts was determined in the course of the first three days; however, in certain cases it was retarded to the 15th day. In the neoplastic mucous membrane an increase in the number of goblet-like cells and their overcrowding with mucus was noted. Residual phenomena in the form of round cell infiltration of the submucosa were detected on the 20th day. No changes in the intestine were subsequently determined.

Among the experimental animals after the administration of the acid, necrosis of the entire mucous membrane, and sometimes also of the submucosa, was observed, and also the formation of a leucocytic projection (Fig. 4). In the course of the first 2 weeks new foci of necrosis appeared as a consequence of the perishing of the old leucocytic projection and the areas of underlying granulation tissue (Fig. 5). At the site of tearing off of the necrotic masses (30th day after the administration of acid) ulcers were left with the formation of granulation tissue at the bottom. The cellular composition of the inflammation infiltrate was gradually changed. In the first day, neutrophil leucocytes predominated, which subsequently underwent breakdown; on the third day macrophages appeared, on the seventh day -- eosinophils, fibroblasts, and then lymphoidal and plasmatic cells appeared. The beginning phenomena of organization of granulation tissue in the form of coarsening of the collagenous fibers, a diminished number of cellular elements, were noted on the 15-25th day; however, in individual animals the process was drawn out until the 50th day. Epithelization of the ulcers began from the third day and ended in general on the 60-80th day. The neoplastic mucous membrane was of irregular thickness; the widened intestinal crypts, containing many goblet-like cells, had an atypical form and were often located in groups in the submucosal layer. Residual phenomena





Fig. 4. Large intestine of a rat injured by  $Sr^{90}$ . First day after administration of acid. Acute inflammation. Necrosis of the mucous and submucosal membranes. Leucocytic infiltration of the muscular layer (staining with hematoxylin-eosin. X 100).

in the form of round cell infiltration of the submucosa, thickening of the muscularis mucosae, and accumulations of macrophages, containing hemosiderin, were observed up to the last period of the investigation. In the areas of the mucous membrane adjacent to the ulcers, destruction of the epithelium, broadening of the lumens of the crypts, and accumulation in them of products of cellular breakdown, were noted. These phenomena subsequently disappeared; however, in the crypts a considerable quantity of goblet-like cells were detected. An inflammatory reaction was also noted in the serous membrane, where sclerotic changes appeared in later periods.

The localization of injuries in the large intestine (the middle or the lower third) corresponded to the location of the catheter, through which the administration of the acid was performed.

A comparison of the changes in the experimental and the control animals showed a different degree of



Fig. 5. Large intestine of a rat injured with Sr<sup>90</sup>. 15th day after the administration of acid. Perishing of an old leucocytic projection and an area of underlying granulation tissue. Formation of a new projection (hematoxylin-eosin stain, X 80).

injury of the large intestine. In the control animals the superficial areas of the mucous membrane were subjected to necrosis; in the animals injured with strontium -- the entire mucous membrane and the submucosal layer were subjected to necrosis. In addition, in the subsequent 15 days in the experimental animals the zone of necrosis was enlarged as a consequence of the perishing of the leucocytic projection and of the section of underlying granulation tissue. The process of tearing off of necrotic masses was retarded up to 30 days. The epithelization lasted until the 60-80th day. In the control rats the restoration of the epithelial cover ended on the fifth day. In both groups of animals the destruction of the epithelium of the crypts in the areas of the mucous membrane adjacent to the zone of necrosis was observed. In the control group it was noted in the course of 15 days, in the experimental animals it was retarded until the end of epithelization of the ulcers. The neoplastic mucous membrane had an irregular thickness; atypical forms

of crypts were encountered in it, which were located in the submucosal layer and were rich in goblet-like cells.

It should also be noted that the changes in the nerve cells of the Auerbach plexus of the stomach and intestine in the control and experimental animals were not identical. Thus, in the rats not injured with strontium, the number of changed neurons was very small and injury of the mucous membrane was only observed in spots; in the experimental animals these disturbances were of a more pronounced character.

In summarizing the results of all three series of experiments, it should be underlined that under conditions of injury of the organism with radiostrontium, the administration into the gastrointestinal tract of a solution of acetic acid evoked in them the development of an acute inflammatory process, which, in spite of certain peculiarities of the course in each section (the stomach, the small and large intestine), was characterized by a number of common factors. All the phases of the inflammatory process in the injured animals were considerably drawn out in time, which led to the prolonged existence and slow healing of the ulcers which formed. A raised vulnerability of the tissues and the formation as a consequence of this of broad foci of necrosis was observed. The fusion and tearing off of necrotic masses was significantly retarded. A slowing and sometimes a distortion of the process of regeneration occurred, as a consequence of which structures atypical for the given organ arose (racemously proliferating glands and goblet-like cells -- in the mucous membrane of the stomach). In certain animals complete epithelization of the ulcers was not observed in the course of the entire period of the investigation.

The results obtained attest to the lowering of the reactivity of the gastrointestinal tract under conditions of injury of the organism by radioactive strontium. The changes in the neural cells of the Auerbach plexus of the stomach and intestine, detected by us, apparently play a definite role in the development of the described disturbances.

In conclusion it should be noted that, in spite of the scantiness of morphological changes, arising in the gastrointestinal tract in the presence of the administration of such a quantity of radioactive strontium, injury of the organism by the indicated isotope leads to the appearance of a certain defectiveness of the course of the inflammatory and reparative processes, which is rather clearly manifested with the aid of the methods which we used.

### Conclusions

1. The reaction of the mucous membrane of the gastro-

intestinal tract to chemical stimulation in the presence of the intraperitoneal administration of  $Sr^{90}$  is characterized by a number of peculiarities: a) in the presence of the action of a chemical stimulant a raised vulnerability of the tissues is observed; b) all phases of the course of the inflammatory process are considerably drawn out in time; c) a retardation, and sometimes also a distortion of the regenerative process, is noted.

2. The changes detected attest to a lowering of the reactivity of the gastrointestinal tract under conditions of injury of the organism due to  $Sr^{90}$ .

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